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APPELLANTS:	Francisco Sanchez-Madrid, *et al.*		
SERIAL NUMBER:	10/770,639	EXAMINER:	Skelding, Zachary S.
FILING DATE:	February 2, 2004	ART UNIT:	1644
FOR:	IMMUNE REGULATION BASED ON THE TARGETING OF EARLY ACTIVATION MOLECULES		

MAIL STOP APPEAL BRIEF–PATENTS
Commissioner for Patents
P.O. Box 1450
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APPEAL BRIEF

Appellants file this Appeal Brief pursuant to 37 C.F.R. § 41.37, in support of their Notice of Appeal, dated March 16, 2010.

The Commissioner is hereby authorized to charge deposit account number 50-0311, Reference No. 33743-501, to cover the fee required under 37 C.F.R. §1.17(c) for filing Appellants' brief. Applicant believes no additional fees are due. However, the Commissioner is hereby authorized to charge any fees that may be due, or credit any overpayment of same, to Deposit Account No. **50-0311**, Reference No. **27331-501 CIP2A**.

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I. STATEMENT OF REAL PARTY IN INTEREST

The real parties in interest are Albor Biologics Inc., assignee, and Medarex, Inc, exclusive licensee.

II. STATEMENT OF RELATED CASES

Appellants know of no other related cases, including any related applications, appeals or interferences, that will directly affect, be directly affected by, or have a bearing on the Board's decision in the pending appeal.

III. STATUS OF CLAIMS

Claims 1-55, 57-58, and 61-104 are canceled.

Claims 56, 59, 60, and 105-115 are pending. Claims 109-115 are withdrawn from consideration. Claims 56, 59, 60, and 105-108 are rejected.

IV. STATUS OF AMENDMENTS

No claim amendments were submitted after the final rejection mailed July 17, 2009.

V. SUMMARY OF THE CLAIMED SUBJECT MATTER

Independent claim 56 recites a method of treating a subject having rheumatoid arthritis comprising administering to the subject an effective amount of a depleting anti-CD69 antibody molecule, wherein the anti-CD69 antibody specifically binds SEQ ID NO: 2. SEQ ID NO: 2 is an amino acid sequence of human CD69.

Depleting anti-CD69 antibody molecules are broadly referred to in the Specification as "antibody molecules which bind CD69 and deplete CD69 expressing cells."[1/] The Specification also provides an example that distinguishes the *in vivo* effect of a depletor antibody from an antibody that merely antagonizes, tolerizes, or neutralizes CD69 expressing cells. Using a collagen-induced arthritis (CIA) model in DBA1 wild type mice, the Specification shows that a depleting anti-CD69 antibody molecule ameliorates collagen-induced arthritis *in vivo,* whereas a

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1/ *See e.g.*, Specification at page 7, beginning at line 22.

non-depleting anti-CD69 antibody molecule exacerbated collagen-induced arthritis. Specially, Example 6 of the Specification [2/] provides as follows (emphasis added):

> The effect of *in vivo* treatment with anti-CD69 antibody has been analyzed using two different anti-CD69 antibodies, mAb 2.2 and mAb 2.3, in the [collagen-induced arthritis (CIA)] model in DBA1 wild type mice.
>
> **MAb 2.2 behaves *in vitro* as a non-depletor antibody.** An IgG1, it is unable to bind complement and does not lyse CD69 expressing cells in an *in vitro* chromium assay (not shown). Furthermore, mAb 2.2 does not induce TGF-b synthesis *in vitro* in the absence of crosslinking (Esplugues *et al.* 2003. J. Exp. Med. 197:1093; Sancho 2003. J. Clin. Invest. 112:872).
>
> The effect of 2.2 anti-mouse CD69 antibody was analyzed *in vivo* in a model of CIA in DBA/1 mice. *In vivo* treatment with this antibody leads to the complete loss of expression of CD69 in populations that express the molecule, such as $CD3^{hi}$ thymocytes (FIG. 22). As shown in the upper right quadrant of the left panel, 14.2% of thymocytes express CD69. Following mAb 2.2 treatment, only 0.9% express CD69 (upper right quadrant, right panel). However, the total thymocyte pool remains constant, since the sums of the upper quadrants in each panel are the same, namely 20.7% (6.5+14.2 for control and 19.8+0.9 for treated). **This shows that mAb 2.2 does not mediate depletion of CD69+ cells *in vivo*. Further studies show that mAb 2.2 removes CD69 from the cell surface, i.e., antagonizes by down-modulation of CD69.**
>
> The treatment of CIA-induced DBA/1 mice with mAb 2.2 significantly exacerbated CIA when administered at days 20 and 28 during the initiation of the secondary response (FIG. 23), in agreement with our results in CD69-deficient mice (FIG. 1).
>
> * * *
>
> **MAb 2.3 behaves *in vitro* as a depletor antibody.** As an IgG2a, it binds complement and lyses CD69-expressing cells in an *in vitro* chromium assay (not shown).
>
> The effect of mAb 2.3 was also analyzed *in vivo* in a model of CIA in DBA/1 mice. *In vivo* treatment with this antibody leads to the depletion of CD69-expressing $CD3^{hi}$ thymocytes (FIG. 24). As shown in the upper right quadrant of the left panel, in this experiment 16.7% of thymocytes express CD69. Following mAb 2.3 treatment, only 0.1% express CD69 (upper right quadrant, right panel). However, the total thymocyte pool is strongly reduced, since the sums of the upper panels are now different, namely 24.8% in the control, but only 8.3% in the treated group. This shows that mAb 2.3 has depleted all CD69-expressing cells, rather than functionally `blocking` CD69.

2/ Specification at page 104, line 14 to page 106, line 2.

> The treatment of CIA-induced DBA/1 mice with mAb 2.3 significantly reduced CIA when administered at days 20 and 28 during the initiation of the secondary response (FIG. 25).
>
> **These results show that the treatment with a down-modulating anti-CD69 could be useful to enhance certain immune responses. In contrast, the depletion of CD69 expressing cells may ameliorate diseases mediated by the activation of the immune system.**

Dependent claim 60 (dependent from claim 59, which is dependent from claim 56) specifies a human anti-CD69 monoclonal antibody as the "depleting anti-CD69 antibody molecule" to be used in the method of claim 56. Human anti-CD69 monoclonal antibodies are described on pages 64 and 65 of the specification.

Independent claim 105 recites a method of treating a subject having rheumatoid arthritis comprising administering to the subject an effective amount of a depleting anti-CD69 antibody molecule that specifically binds SEQ ID NO:2, wherein the depleting anti-CD69 antibody molecule may be conjugated to a second therapeutic agent. Claim 105 differs from claim 56 in that it indicates that a second therapeutic agent may be conjugated to depleting anti-CD69 antibody molecule. Antibody molecule conjugates are described in the specification in the section beginning on page 68, line 11.

VI. GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

The following issue is on appeal:

Whether the rejection of claims 56, 59, 60, and 105-108 under 35 U.S.C. § 103(a) citing Choy 1998[3/] as the primary reference in view of Marzio,[4/] Black,[5/] McInnes 1997,[6/] McInnes 1998,[7/] Strom,[8/] and White[9/] is proper. This rejection is set forth in the Non-Final Office Action mailed December 1, 2009, hereinafter the "Office Action".

VII. STATEMENT OF FACTS

A. Teachings from the primary reference, Choy 1998

The primary reference Choy 1998[10/] summarizes the results of clinical trials involving the use of depleting anti-CD4 monoclonal antibodies and non-depleting monoclonal antibodies for the treatment of rheumatoid arthritis. Choy 1998 states in the Abstract that the use of depleting anti-CD4 antibodies "in rheumatoid arthritis had been abandoned." Choy 1998 also states in the Abstract that "clinical trials of non-depleting anti-CD4 monoclonal antibodies in rheumatoid arthritis showed that they could suppress synovitis" and on page 488, right column, lines 10-12 states that T-cell depletion strategies have been abandoned in favour of a strategy aiming to tolerize T cells."

Choy 1998 also notes that the administration of depleting anti-CD4 antibody resulted in and "unacceptable level of immunosuppression" and that "[t]his principle is likely to apply to all

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3/ *Br J Rheumatol.* 1998 May; 37(5):484-90. Review.

4/ *Immunopharmacol Immunotoxicol.* 1999 Aug; 21 (3):565-82.

5/ *Arthritis Res.*, 2002; 4(3): 177-83.

6/ *Nat Med.* 1997 Feb; 3(2):189-95.

7/ *Immunol Today.* 1998 Feb; 19(2):75-9.

8/ U.S. Patent Publication No. 2002/0114781.

9/ U.S. Patent Publication No. 2002/0039557.

10/ Choy *et al.*, Br J Rheumatol. 1998 May;37(5):484-90. Review.

depleting anti-T-cell [monoclonal antibodies]". [11/] The following excerpt from Choy 1998 summarizes this point:[12/]

> Among the synovial CD4+ lymphocytes, most are recruited non-specifically to the joint and only a small proportion are the disease driving arthritogenic lymphocytes. Therefore, if one aims to improve arthritis by depleting synovial CD4+ lymphocytes, sufficiently high doses must be given to achieve significant concentration in the joint. However, at these doses of depleting mAbs, there may be severe depletion of peripheral CD4+ lymphocytes for a prolonged period, resulting in an unacceptable level of immunosuppression. This principle is likely to apply to all depleting anti-T-cell mAbs. Therefore, the T-cell-depletion strategy has been abandoned in favour of a strategy aiming to tolerize T cells.

Choy 1998 does not teach specifically targeting the depletion of $CD69^+$ cells in the treatment of any disease. Choy 1998 does not teach the development of any depleting anti-CD69 antibody or any use of a depleting anti-CD69 antibody.

B. McInnes 1998

McInnes 1998[13/] is a review article entitled: "Interleukin 15: A Proinflammatory Role in Rheumatoid Arthritis." McInnes 1998 "reviews data which demonstrate that synovial T-cell recruitment and activation can occur as a result of local synthesis of IL-15, and that such non-specific activation can result in perpetuation of inflammation through induction of [TNF-α] synthesis via a cell-contact-dependent pathway." [14/] McInnes 1998 reviews studies teaching that IL-15 or IL-15 receptors may be targeted to *inhibit* T-cell activation and *interfere* with their membrane interactions. Specifically, McInnes 1998 teaches that "IL-15 can recruit T cells and … modify cell-cell interactions within inflammatory sites,"[15/] that IL-15 expression is associated with rheumatoid arthritis,[16/] and that "IL-15 can recruit and expand CD45R0+ memory cell

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11/ See Choy 1998 at page 488, right column, lines 9-12.

12/ See Choy 1998 at page 488, left column, last two lines, to right column, line 12.

13/ *Immunol Today*. 1998 Feb; 19(2):75-9.

14/ McInnes 1998 at page 75, right column, lines 16-20.

15/ McInnes 1998 at page 76, left column, lines 32-34.

16/ McInnes 1998 at Title. See also the entire document.

subsets in the synovial membrane, in which, … newly recruited T-cells can produce TNF-α directly or via contact with macrophages."[17/]

McInnes 1998 provides a commentary that begins on page 77, left column with the heading "A critical role for IL-15 in synovial inflammation;" this section includes citations to both McInnes 1997, cited in the present rejection, and also Choy *et al.*, *Arthritis Rheum.* 1996; 39: 52-56 (hereinafter "Choy 1996"), which is a precursor paper to the primary reference Choy 1998. In this commentary, McInnes 1998 provides, in part, as follows (emphasis added):

> [D]iverse cell types within synovial membrane may exhibit coordinate proinflammatory activities through cell contact. … T-cell-directed therapies that not only *inhibit* T-cell activation but also *deplete* T cells from the synovial compartment, or at least *interfere* with their membrane interactions, will probably be the most efficacious. It is *of interest* that clinical improvement following CD4 therapy in RA correlates with synovial T-cell coating with anti-CD4. *Citing* Choy 1996[18/].

The study "of interest" cited in this passage is Choy 1996, which showed that the percentage of anti-CD4 monoclonal antibody-coated lymphocytes in the rheumatoid joint may be associated with clinical improvement.

Further, McInnes 1998 concludes the following on page 78 under the heading "Therapeutic Implications":

> The identification of IL-15-mediated T-cell and monocyte activation in the synovial membrane, … provides a novel target for such biological approaches. This might be either through direct neutralization of IL-15 or by targeting IL-15 receptors.

CD69 is not discussed under this heading related to "Therapeutic Implications." In fact, McInnes 1998 does not teach specifically targeting the depletion of $CD69^+$ cells in the treatment of any disease. McInnes 1998 does not teach the development of any depleting anti-CD69 antibody or any use of a depleting anti-CD69 antibody. The examiner acknowledges that McInnes 1998 does not teach the use of a depleting anti-CD69 antibody to treat rheumatoid arthritis.[19/]

17/ McInnes 1998 at page 77, left column, lines 17-20.

18/ Choy et al., *Arthritis Rheum.* 39, 52-56 (1996).

19/ Final Office Action mailed August 15, 2007, page 5, fifth (5th) full paragraph.

C. McInnes 1997

McInnes 1997 teaches that peripheral blood T-cells and U937 cells that are co-cultured in the presence of IL-15 *in vitro* have decreased TNFα production when treated with a *neutralizing* antibody to CD69.[20/] There are no teachings in McInnes 1997 that these antibodies deplete the cultures of $CD69^+$ cells. McInnes 1997 does not suggest down regulation of CD69. McInnes 1997 does not teach specifically targeting the depletion of $CD69^+$ cells in the treatment of any disease. McInnes 1997 does not teach the development of any depleting anti-CD69 antibody or any use of a depleting anti-CD69 antibody. The examiner acknowledges that McInnes 1997 does not teach the use of a depleting anti-CD69 antibody to treat rheumatoid arthritis.[21/]

D. Marzio

Marzio is a review article entitled: "CD69 and Regulation of the Immune Function." Marzio teaches that CD69 has a "wide cellular distribution". [22/] Specifically, Marzio teaches that "CD69 is constitutively expressed by monocytes, platelets, $CD3^{bright}$ thymocytes, and some peripheral lymphocyte populations." [23/] Marzio teaches that "CD69 represents a cell activation antigen in a wide variety of hematopoietic lineages, including T and B lymphocytes, NK cells, neutrophils, eosinphils, and murine macrophages." [24/]

In the context of disease, Marzio teaches that CD69 is absent on peripheral blood resting lymphocytes and that $CD69^+$ T cells can be detected at high levels in the synovial fluid and synovial membrane from chronic rheumatoid arthritis patients. [25/]

A distinction can be made between CD69 expression patterns on resting peripheral T cells and activated peripheral T cells. Marzio teaches that "[r]esting lymphocytes do not express CD69, but it represents the earliest activation marker" and that "circulating T and NK cells have

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20/ *See* McInnes 1997 at page 193, Figure 7 legend.

21/ Final Office Action mailed August 15, 2007, page 5, fifth (5^{th}) full paragraph.

22/ Marzio at page 565, at Abstract, third paragraph.

23/ Marzio at page 567, beginning at first paragraph under the heading "CD69 Expression by Different Cell Types".

24/ Marzio at page 568, lines 2-5.

25/ See Marzio at page 572, lines 2-5, first full paragraph under the heading "CD69 in Disase."

also been found to be $CD69^+$, probably as a result of *in vivo* activation." [26/] Thus, activated peripheral T cells can express CD69 whereas it is believed that resting peripheral T cells do not.

Marzio does not teach the depletion of $CD69^+$ cells in the treatment of any disease. Marzio does not teach the development of any depleting anti-CD69 antibody or any use of a depleting anti-CD69 antibody.

E. Black

Black provides the results and conclusions from a study "done to determine if the differentiation and activation phenotype of T cells in synovial fluid (SF) from patients with juvenile idiopathic arthritis (JIA) is associated with T-cell proliferation." [27/] The Office Action in the paragraph spanning page 4 and 5 characterizes the teachings of Black as follows:

> Furthermore, in this regard one of ordinary skill in the art knows that not only do peripheral blood *resting* lymphocytes *not* express CD69 as taught by Marzio, but also peripheral memory T-cells (CD45RO+) and activated T cells (HLA-DR) *also do not express* CD69 as shown in Figures 1 and 2 of Black.

In fact, Black does not report that activated T cells do not express CD69, but rather reports that "[t]here was a greater expression of the activation markers CD69, HLA-DR, CD25 and CD71 on T cells from SF than on those from the peripheral blood" in subjects with juvenile idiopathic arthritis. [28/]

Black does not teach specifically targeting the depletion of $CD69^+$ cells in the treatment of any disease. Black does not teach the development of any depleting anti-CD69 antibody or any use of a depleting anti-CD69 antibody.

F. Strom

Strom does not teach specifically targeting the depletion of $CD69^+$ cells in the treatment of any disease. Strom does not teach the development of any depleting anti-CD69 antibody or any use of a depleting anti-CD69 antibody. Rather, Strom provides a general description related to agents that are target cell depleting for an interleukin- or interleukin receptor-bearing (*e.g.*, IL-

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[26/] Marzio at page 568, second full paragraph, lines 1-8.

[27/] Black at Abstract, lines 1-2.

[28/] Black at Abstract, lines 7-9.

2 and IL-15R) cell.[29/] The Office Action at page 6, forth paragraph cites to paragraphs 54-55 and 64-68 of Strom. CD69 is never mentioned in these passages.

G. White

White does not teach specifically targeting the depletion of $CD69^+$ cells in the treatment of any disease. White does not teach the development of any depleting anti-CD69 antibody or any use of a depleting anti-CD69 antibody. Rather, White concerns the treatment of B-cell malignancies with radiolabeled anti-CD20 antibodies.[30/] The Office Action at page 6, forth paragraph cites to claim 3 and paragraphs 0026, 0075, and 0217-0219 of White. CD69 is never mentioned in these passages.

VIII. ARGUMENT

A. The Prior Art Teaches away from the Claimed Invention

It is improper to combine references where the references teach away from their combination.[31/] The Supreme Court's discussion of Adams[32/] in KSR, 550 U.S. at 416 cements the teaching away doctrine as a viable rebuttal to an obviousness rejection.

> In *United States v. Adams,* 383 U.S. 39, 40, 86 S.Ct. 708, 15 L.Ed.2d 572 (1966), a companion case to *Graham,* the Court considered the obviousness of a "wet battery" that varied from prior designs in two ways: It contained water, rather than the acids conventionally employed in storage batteries; and its electrodes were magnesium and cuprous chloride, rather than zinc and silver chloride. The Court recognized that when a patent claims a structure already known in the prior art that is altered by the mere substitution of one element for another known in the field, the combination must do more than yield a predictable result. 383 U.S. at 50-51, 86 S.Ct. 708. It nevertheless rejected the Government's claim that Adams's battery was obvious. The Court relied upon the corollary principle that when the prior art ***teaches away*** from combining certain known elements, discovery of a successful means of combining them is more likely to be nonobvious. *Id.* at 51-52, 86 S.Ct. 708. When Adams designed his battery, the prior art warned that risks were involved in using the types of electrodes he employed. The fact that the elements worked together in an unexpected and

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29/ Strom at paragraphs 54 and 55.

30/ White at paragraph 26.

31/ See M.P.E.P. § 2145(X)(D)(2), *citing In re Grasselli*, 713 F.2d 731, 743, 218 USPQ 769, 779 (Fed. Cir. 1983).

32/ *United States v. Adams,* 383 U.S. 39, 40, 86 S.Ct. 708, 15 L.Ed.2d 572 (1966).

> fruitful manner supported the conclusion that Adams's design was not obvious to those skilled in the art. *KSR v. Teleflex*, 550 U.S. at 416 (emphasis added here).

To prevail in showing that a reference teaches away, the applicant must demonstrate a clear discouragement from following the teachings within the reference to pursue the claimed invention. *In re Kahn*, 441 F.3d 977 (Fed. Cir. 2006). *In re Kahn* was recently applied by the Board in *Ex parte Rambaud*, where the Appellants prevailed by showing that the prior art taught away from the Appellants' claimed invention. 2008 WL 4928400 (Bd. Pat. App. & Int. 2008). The invention was directed to a method of transmitting data using a frequency-hopping scheme by sending "padding data" between frequency shifts. The prior art taught a communications system that transmitted data using a frequency hopping scheme where the frequency shifts occurred at fixed interval times determined by the operator. During the shift in frequency, no data is sent/received. After the time determined by the operator elapses, data may be sent again. The second prior art reference taught the inclusion of a time guard intervals (or cyclic prefix) to eliminate distortion during data transmission.

The Examiner asserted that it would have been obvious to insert "padding data" during the interval when no data is sent based on the use of the time guard intervals. However, the Appellant argued that the prior art expressly stated that no data is sent during a fixed interval determined by the operator. As such, a person of ordinary skill in the art would have no reason or motivation to send any data during the time the frequency is shifting due to inherent instability of transmission during frequency shift. The Board agreed and reversed the Examiner's rejection because the prior art reference would have led one of ordinary skill in the art "in a direction divergent from the path that was taken by the applicant." *In re Kahn*, 441 F.3d 977, 990 (Fed. Cir. 2006).

1. ***Choy 1998* Provides a Clear Discouragement From Using Any Depleting Monoclonal Antibodies in the Treatment of Rheumatoid Arthritis**

In the present case, the primary reference Choy 1998[33/] contains a clear discouragement from the use of any depleting monoclonal antibody in the treatment of rheumatoid arthritis. Choy 1998 summarizes the results of clinical trials involving the use of depleting anti-CD4

33/ Choy *et al.*, Br J Rheumatol. 1998 May;37(5):484-90. Review.

monoclonal antibodies and non-depleting monoclonal antibodies for the treatment of rheumatoid arthritis. Choy 1998 states in the Abstract that the use of depleting anti-CD4 antibodies "in rheumatoid arthritis had been abandoned" and also provides that "clinical trials of non-depleting anti-CD4 monoclonal antibodies in rheumatoid arthritis showed that they could suppress synovitis." Choy 1998 goes further and recommends the general strategy that T-cell depletion strategies should be abandoned in favor of a strategy aiming to tolerize T cells. [34/]

In this manner, Choy 1998 expressly teaches that no depleting antibody should be used for treating rheumatoid arthritis, but rather non-depleting antibodies should be used as part of "a strategy aiming to tolerize T cells" as "non-depleting anti-CD4 monoclonal antibodies in rheumatoid arthritis showed that they could suppress synovitis."[35/] The teaching away in Choy 1998 from using depleting antibodies is made expressly clear and teaches that the negative effects seen with the use of depleting anti-CD4 antibody "is likely to apply to all depleting anti-T-cell [monoclonal antibodies]". Specifically, Choy 1998 states the following:[36/]

> Among the synovial CD4+lymphocytes, most are recruited non-specifically to the joint and only a small proportion are the disease driving arthritogenic lymphocytes. Therefore, if one aims to improve arthritis by depleting synovial CD4+lymphocytes, sufficiently high doses must be given to achieve significant concentration in the joint. However, at these doses of depleting mAbs, there may be severe depletion of peripheral CD4+ lymphocytes for a prolonged period, resulting in an unacceptable level of immunosuppression. **This principle is likely to apply to all depleting anti-T-cell mAbs. Therefore, the T-cell-depletion strategy has been abandoned in favour of a strategy aiming to tolerize T cells.**

The weight of the evidence cited by the Examiner would not have directed a person of ordinary skill in the art to use depleting anti-CD69 antibodies to treat rheumatoid arthritis at least because Choy 1998 provides a clear discouragement for the use of any and all depleting antibodies "in favor of a strategy to tolerize T cells."[37/] Accordingly, Choy 1998 is not properly combinable with any reference in order to establish that a person of ordinary skill in the art

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34/ See Choy 1998 at page 488, right column, lines 10-12

35/ See Choy 1998 at Abstract.

36/ See Choy 1998 at page 488, left column, last two lines, to right column, line 12.

37/ See Choy 1998 at page 488, right column, line 12.

would have modified the teaching of Choy 1998 to use depleting anti-CD69 antibodies to treat rheumatoid arthritis.

2. ***The Cited References Lead One of Ordinary Skill in the Art in a Direction Divergent From the Use of Depleting Anti-CD69 Antibodies in the Treatment of Rheumatoid Arthritis***

Further, the cited references lead one of ordinary skill in the art in a direction divergent from the path that was taken by the appellant. Depletion therapy using an anti-CD69 antibody is never contemplated in any of the cited references. Indeed, none of the cited references teach or suggest the existence of or any use of depleting anti-CD69 antibodies. For example, Choy 1998 concerns anti-CD4 antibodies and recommends the use of non-depleting anti-CD4 antibodies. McInnes 1997 and McInnes 1998 are concerned with elucidating the role IL-15 in rheumatoid arthritis, not developing CD69 as a target. Marzio and Black discuss the expression patterns of CD69 in disease and make no definitive statements with regard to treatment strategies. None of the cited references teach or suggest a depleting anti-CD69 antibody or any use thereof.

McInnes 1997 discloses a non-depleting, neutralizing CD69 antibody used, not for treatment, but as part of an experiment to elucidate the role of IL-15 in T-cell and monocyte activation in the synovial membrane. Even assuming, *arguendo*, that a person of ordinary skill in the art would have been motivated[38/] to combine the cited references, the combination of the teachings at best directs a person of ordinary skill in the art to the use of a non-depleting, neutralizing (or tolerizing) antibody. For example, the combination at best provides the treatment of rheumatoid arthritis with an antibody that "tolerizes T cells", as suggested by Choy 1998, with the non-depleting, neutralizing CD69 antibody disclosed by McInnes 1997. This is NOT the subject of the present claims and indeed is a direction divergent from the path taken by the Appellant.

The present claims are directed to the use of depleting anti-CD69 antibodies, which are shown to provide a more desirable result as compared to a non-depleting, neutralizing (or tolerizing) anti-CD69 antibody. In contrast to the teachings of Choy 1998, the present specification includes data from an *in vivo* model for unwanted immune response that shows that it is important that the CD69 specific antibody be a depletor anti-CD69 antibody, as opposed to a

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38/ Applicants do not concede that there was sufficient motivation.

non-depleting or tolerizing antibody. Treatment of mice having collagen-induced arthritis (CIA) with a non-depleting CD69 specific antibody that does not deplete CD69+ cells in vivo (i.e., mAb 2.2) actually exacerbated CIA in those mice.[39/]

The Examiner argues that McInnes 1998[40/] provides one of ordinary skill in the art to pursue depletion strategies. To support this premise, the Examiner cites to the following passage of McInnes 1998 that provides, in part, as follows (emphasis added):

> [D]iverse cell types within synovial membrane may exhibit coordinate proinflammatory activities through cell contact. … T-cell-directed therapies that not only *inhibit* T-cell activation but also *deplete* T cells from the synovial compartment, or at least *interfere* with their membrane interactions, will probably be the most efficacious. It is *of interest* that clinical improvement following CD4 therapy in RA correlates with synovial T-cell coating with anti-CD4. *Citing* Choy 1996.[41/]

When this passage is read in context of the entirety of McInnes 1998, however, it becomes clear that McInnes 1998 is referring to IL-15 and/or CD4 as the targets for therapy, thereby teaching away from CD69. Indeed, the primary reference of Choy 1998 is actually the follow-on paper to Choy 1996, cited in the above passage of McInnes 1998. Thus, Choy 1998 is reporting on the results of the study that was "of interest" to McInnes 1998. Choy 1998, beginning at page 488, left column, second full paragraph, further explains the study of Choy 1996 and, as presented above, concludes at page 488, right column, lines 5-12, that T-cell depletion strategies should be abandoned in favor of a strategy aiming to tolerize T cells. In this manner, Choy 1998 teaches away from the teachings in McInnes 1998 relied on in the Office Action.

Additionally, McInnes 1998 is a review article that reviews studies teaching or suggesting that IL-15 or IL-15 receptors may be targeted to *inhibit* T-cell activation and *interfere* with their membrane interactions. CD69 is never referred to as a therapeutic target. Specifically, McInnes 1998 teaches that "IL-15 can recruit T cells and … modify cell-cell interactions within

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39/ *See e.g.*, Specification at page 105, lines 3-6.

40/ *Immunol Today.* 1998 Feb; 19(2):75-9.

41/ Choy et al., *Arthritis Rheum.* 39, 52-56 (1996).

inflammatory sites,"[42/] that IL-15 expression is associated with rheumatoid arthritis,[43/] and that "IL-15 can recruit and expand CD45R0+ memory cell subsets in the synovial membrane, in which, … newly recruited T-cells can produce TNF-α directly or via contact with macrophages."[44/]

In this manner, the examiner exaggerates and overemphasizes isolated teachings of the prior art references by not considering the references as a whole, which is improper. It is well established that reliance on isolated teachings in the prior art that fails to consider the reference as a whole is improper. The Federal Circuit in Bausch & Lomb v. Barnes-Hind/Hydrocurve, Inc.[45/] clearly instructs that cited references must be considered for all they teach, and not relied on to make "strawman" arguments that highlight an isolated teaching of the reference. This point is restated in MPEP § 2141.02 (VI) as follows: "A prior art reference must be considered in its entirety, *i.e.*, as a whole, including portions that would lead away from the claimed invention." The examiner fails to consider the cited references in their entirety.

B. The Office Action Fails To Establish a Finding of Some Teaching, Suggestion, or Motivation To Combine the Cited References and Fails To Establish a Reasonable Expectation of Success

As a result of *KSR*, the PTO promulgated examination guidelines "to assist USPTO personnel to make a proper determination of obviousness." 72 Fed. Reg. 57,526 (Oct. 10, 2007). As part of the Examination Guidelines, the PTO set forth several rationales to support rejections under 35 U.S.C. § 103, which are drawn from and closely track the language of the *KSR* decision. *Id.* at 57,529. Based on the Appellants' analysis of the rejection set forth in the Office Action, it is believed that the Examiner is setting forth a teaching, suggestion, or motivation (TSM) rationale. If an Examiner uses the TSM test to reject a claimed invention under § 103, the Examiner must articulate the following:

42/ McInnes 1998 at page 76, left column, lines 32-34.

43/ McInnes 1998 at Title. See also the entire document.

44/ McInnes 1998 at page 77, left column, lines 17-20.

45/ 796 F.2d 443, 447-49 (Fed. Cir. 1986), cert. denied, 484 U.S. 823 (1987).

- a finding that there was some teaching, suggestion, or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings;
- a finding that there was a reasonable expectation of success; and
- any additional findings based on the *Graham* factors to explain a conclusion of obviousness.

1. ***No motivation or reasonable expectation of success for using depleting antibodies as a treatment option for rheumatoid arthritis***

Using the above as guidance, Appellants assert that one of ordinary skill in the art would not have had motivation to combine the teachings of Choy 1998, Marzio, Black, McInnes 1997, McInnes 1998, Strom, and White. One of ordinary skill in the art could not find a motivation to combine these references either in the references themselves or in knowledge generally available in the art. Indeed, as explained above, Choy 1998 clearly teaches that depleting antibodies should not be considered as a treatment option for rheumatoid arthritis. None of the other cited references refutes this conclusion. The only other reference to even remark on the use of depletion strategies for the treatment of rheumatoid arthritis is McInnes 1998, and this references refers back to the line of work published by the authors of Choy 1998. Thus, the combination of references actually teaches away from the use of depleting antibodies for the treatment of rheumatoid arthritis.

The *KSR* Court noted that obviousness cannot be proven merely by showing that the elements of a claimed device were known in the prior art; it must be shown that those of ordinary skill in the art would have had some "apparent reason to combine the known elements in the fashion claimed." *Id.* at 1741. In the same way, when the prior art teaches away from the claimed solution as presented here, obviousness cannot be proven merely by showing that a known method could have been modified by routine experimentation or solely on the expectation of success; it must be shown that those of ordinary skill in the art would have had some apparent reason to modify the known method in a way that would result in the claimed composition. See *e.g., Ex parte Whalen*, 89 U.S.P.Q.2d 1078, 1084 (Bd. Pat. App. & Int. 2008)(holding that "obviousness cannot be proven merely by showing that a known composition *could have* been modified by routine experimentation or solely on the expectation of success.")

2. ***No motivation or reasonable expectation of success for substituting non-depleting antibodies with depleting antibodies as a treatment option for rheumatoid arthritis***

The Office Action fails to clearly articulate a reasonable expectation of success as to why depleting anti-CD69 antibodies would have been more suitable to other treatment options, such as antibodies that merely tolerize or neutralize T-cells as suggested in Choy 1998. In this regard, the Office Action merely states that a person of ordinary skill in the art could have manufactured depleting anti-CD69 antibodies. This is improper. See *e.g., Ex parte Whalen*, 89 U.S.P.Q.2d 1078, 1084 (Bd. Pat. App. & Int. 2008)(holding that "obviousness cannot be proven merely by showing that a known composition *could have* been modified by routine experimentation or solely on the expectation of success.").

3. ***No motivation or reasonable expectation of success for manufacturing depleting anti-CD69 antibodies***

The Office Action contends that a person of ordinary skill in the art would have manufactured depleting anti-CD69 antibodies for the purposes of performing the claimed method of treating rheumatoid arthritis. However, none of the cited references teach CD69 as a target for therapy. As explained above, at best the cited references merely establish that CD69 plays a possible role in the progression of the disease. Never is CD69 referred to as a target for therapy.

The Office Action does not provide a persuasive rationale for why a person of ordinary skill in the art would have produced a depleting anti-CD69 antibody. That is, the Office Action merely provides that the person of ordinary skill in the art *could have* manufactured such antibodies. The Office Action fails to provide a reasonable rationale as to why a person of ordinary skill in the art would have manufactured a new class of depleting anti-CD69 antibodies, especially in view of the teachings in the art that non-depleting antibodies are more suitable for the treatment of rheumatoid arthritis.

C. The Examiner Has Not Properly Established That One Of Ordinary Skill In The Art Could Have Substituted Depleting CD4 Antibodies With Depleting CD69 Antibodies Resulting In A Predictable Outcome, and Thus, This Rationale Fails

As a result of *KSR*, the PTO promulgated examination guidelines "to assist USPTO personnel to make a proper determination of obviousness." 72 Fed. Reg. 57,526 (Oct. 10, 2007). As part of the Examination Guidelines, the PTO set forth several rationales to support rejections under 35 U.S.C. § 103, which are drawn from and closely track the language of the *KSR*

decision. *Id.* at 57,529. Based on the Appellants analysis of the rejection set forth in the Office Action, it is believed that the Examiner is not setting forth the rationale that a claimed invention is obvious when one of the claimed element is substituted for another known element in the prior art and the combination yields a predictable result. To find a claimed invention as obvious when one of the claimed element is substituted for another known element in the prior art and the combination yields a predictable result, an Examiner must articulate the following: [46/]

- a finding that the difference between the claimed invention and the prior art is a substitution of some component(s) for (an)other component(s);
- a finding that the substituted components and their functions were known in the art;
- a finding that one of ordinary skill in the art could have substituted one known element for another resulting in a predictable outcome; and
- any additional findings based on the *Graham* factors to explain a conclusion of obviousness.

As applied to the present facts, it is noted that none of the cited references teach or disclose the use of a depleting anti-CD69 antibody and therefore there can be no finding that the substituted components (i.e., a depleting anti-CD69 antibody) and their functions were known in the art. According, use of this rationale for obviousness cannot support a *prima facie* case of obviousness.

D. Any *Prima Facie* Case of Obviousness is Rebutted By Evidence of Unexpected Results Set Forth in the Specification

Appellants submit, as explained above, that the Examiner has not established a *prima facie* case of obviousness. However, even if the Examiner had presented such a case (Appellants submit that the Examiner did not present such a case), this case would be rebutted by the unexpected results presented in the instant application. As set forth in *KSR*, "combining elements that work together 'in an unexpected and fruitful manner' would not have been obvious."[47/]

46/ 72 Fed. Reg. 57,526 (Oct. 10, 2007) at 57,529.

47/ KSR, 127 S. Ct. at 1740.

Appellants submit that the methods of claims 56, 59, 60, 67-69, and 105-108 are based upon unexpected results that shows that depleting anti-CD69 antibody molecules are effective in an *in vivo* model for unwanted immune response. The specification teaches, unexpectedly from the standpoint of one of ordinary skill in the art at the time the invention was made, that it is important that the CD69 specific antibody be a depletor of CD69+ cells, as opposed to specifically binding to CD69, while not depleting CD69+ cells in an *in vivo* model for unwanted immune response. Treatment of mice having an unwanted immune response (*i.e.*, collagen-induced arthritis (CIA)) with a CD69 specific antibody that does not deplete CD69+ cells *in vivo* (*i.e.*, mAb 2.2) actually exacerbated CIA in those mice.[48/] In contrast, treatment of CIA induced mice with a CD69 specific antibody that depletes CD69+ cells (*i.e.*, mAb 2.3) significantly reduced CIA.[49/] In this sense, the neutralizing antibodies of McInnes 1997 may actually exacerbate rheumatoid arthritis if they do not deplete CD69+ cells. This result was unexpected in light of cited references. Thus, Appellants submit that the methods of claims 56, 59, 60, 67-69 and 105-108 are based on unexpected properties and thus are non-obvious over Choy 1998, Marzio, Black, McInnes 1997, McInnes 1998, Strom, and White.

The Examiner rebuts the Appellants findings of unexpected results by citing McInnes 1998. Specifically, the Examiner cites to a passage in McInnes 1998 that provides, in part, as follows (emphasis added):

> [D]iverse cell types within synovial membrane may exhibit coordinate proinflammatory activities through cell contact. … T-cell-directed therapies that not only *inhibit* T-cell activation but also *deplete* T cells from the synovial compartment, or at least *interfere* with their membrane interactions, will probably be the most efficacious. It is *of interest* that clinical improvement following CD4 therapy in RA correlates with synovial T-cell coating with anti-CD4. *Citing* Choy 1996[50/].

This passage, however, refers to T-cell depletion strategies in general and specifically mentions anti-$CD4^+$ T-cell depletion studies that is the subject of the primary reference Choy 1998. Indeed, the study "of interest" cited in this passage is Choy 1996, which is a precursor paper to the primary reference Choy 1998. In fact, McInnes 1998 never discusses CD69 as a

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48/ *See e.g.*, Specification at page 105, lines 3-6.

49/ *See e.g.*, Specification at lines 27-29 and Figure 25.

50/ Choy et al., *Arthritis Rheum.* 39, 52-56 (1996).

target for therapy. Further, Choy 1996 and Choy 1998 actually support the Appellants position that the results indicating that the use of depleting anti-CD69 antibodies to ameliorate an arthritic condition would have been unexpected. The evidence presented by the Examiner is insufficient to overcome Appellants' evidence of unexpected results.

IX. CONCLUSION

Reversal of the rejection is respectfully requested.

Respectfully submitted,

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X. CLAIMS APPENDIX

1-55. **(Canceled)**

56. **(Rejected; Previously Presented)** A method of treating a subject having rheumatoid arthritis comprising administering to the subject an effective amount of a depleting anti-CD69 antibody molecule, wherein the anti-CD69 antibody molecule specifically binds SEQ ID NO:2.

57-58. **(Canceled)**

59. **(Rejected; Previously Presented)** The method of claim 56, wherein said depleting anti-CD69 antibody molecule is selected from the group consisting of: a humanized anti-CD69 antibody molecule, a human anti-CD69 antibody molecule, a chimeric anti-CD69 antibody molecule and a deimmunized anti-CD69 antibody molecule.

60. **(Rejected; Original)** The method of claim 59, wherein said human anti-CD69 antibody molecule is a monoclonal antibody.

61-104. **(Canceled)**

105. **(Rejected; Previously Presented)** A method of treating a subject having rheumatoid arthritis comprising administering to the subject an effective amount of a depleting anti-CD69 antibody molecule, wherein the anti-CD69 antibody molecule specifically binds SEQ ID NO:2, alone or conjugated to a second therapeutic agent.

106. **(Rejected; Original)** The method of claim 105, wherein said second therapeutic agent is selected from the group consisting of: chemotherapeutic agents; radioisotopes; and cytotoxins.

107. **(Rejected; Previously Presented)** The method of claim 105, wherein the antibody molecule is a monoclonal antibody.

108. **(Rejected; Original)** The method of claim 107, wherein the monoclonal antibody is a human antibody.

109. **(Withdrawn)** A method of treating a subject having viral chronic hepatitis comprising administering to the subject an effective amount of a depleting anti-CD69 antibody molecule, wherein the anti-CD69 antibody molecule specifically binds SEQ ID NO:2.

110. **(Withdrawn)** The method of claim 109, wherein said depleting anti-CD69 antibody molecule is selected from the group consisting of: a humanized anti-CD69 antibody molecule, a human anti-CD69 antibody molecule, a chimeric anti-CD69 antibody molecule and a deimmunized anti-CD69 antibody molecule.

111. **(Withdrawn)** The method of claim 110, wherein said human anti-CD69 antibody molecule is a monoclonal antibody.

112. **(Withdrawn)** A method of treating a subject having viral chronic hepatitis comprising administering to the subject an effective amount of a depleting anti-CD69 antibody molecule, wherein the anti-CD69 antibody molecule specifically binds SEQ ID NO:2, alone or conjugated to a second therapeutic agent.

113. **(Withdrawn)** The method of claim 112, wherein said second therapeutic agent is selected from the group consisting of: chemotherapeutic agents; radioisotopes; and cytotoxins.

114. **(Withdrawn)** The method of claim 112, wherein the antibody molecule is a monoclonal antibody.

115. **((Withdrawn)** The method of claim 114, wherein the monoclonal antibody is a human antibody.

XI. EVIDENCE APPENDIX

Evidence Entered by the Examiner

1. McInnes *et al.,* IMMUNOL. TODAY 19(2):75-9 (Feb. 1998).

2. McInnes *et al.,* NAT MED. 3(2):198-95 (Feb. 1997).

3. Choy *et al.*, BR J RHEUMATOL. 1998 May;37(5):484-90. Review.

4. Marzio *et al.*, IMMUNOPHARMACOL IMMUNOTOXICOL. 1999 Aug; 21 (3):565-82.

5. Black *et al.*, ARTHRITIS RES., 2002; 4(3): 177-83.

6. Strom *et al.*, U.S. Patent Publication No. 2002/0114781.

7. White *et al.*, U.S. Patent Publication No. 2002/0039557.

Evidence Relied Upon by Appellant

8. Choy *et al.*, ARTHRITIS RHEUM. 1996 Jan;39(1):52-6.

9. Examination Guidelines, 72 Fed. Reg. 57,526 (Oct. 10, 2007).

10. KSR Int'l Co. v. Teleflex Inc., 127 S. Ct. 1727, 82 USPQ2d 1385 (2006).

11. United States v. Adams, 383 U.S. 39, 40, 86 S.Ct. 708, 15 L.Ed.2d 572 (1966)

12. In re Grasselli, 713 F.2d 731, 743, 218 USPQ 769, 779 (Fed. Cir. 1983)

13. In re Kahn, 441 F.3d 977 (Fed. Cir. 2006)

14. Ex parte Rambaud, 2008 WL 4928400 (Bd. Pat. App. & Int. 2008)

15. Bausch & Lomb v. Barnes-Hind/Hydrocurve, Inc., 796 F.2d 443, 447-49 (Fed. Cir. 1986), cert. denied, 484 U.S. 823 (1987).

16. Ex parte Whalen, 89 U.S.P.Q.2d 1078, 1084 (Bd. Pat. App. & Int. 2008).

XII. RELATED PROCEEDINGS APPENDIX

Appellants know of no other related appeals or interferences which will directly affect, be directly affected by, or have a bearing on the Board's decision in the pending appeal.

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